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Neurobiology of Feeding Behaviour : A Perspective of Last Four Decades*

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Feeding behaviour is regulated by a multiple-sensor, closed-feedback system, with regulated input as well as output. The driving biological need, linked to the internal physiological deficits or biologically relevant events in the external envionment is reflected in the changes in different major homeostatic indices determining the normal metabolism, and interact with the environmental factors to form the basis of the biological motivation. There is a distinct relationship between sensations (e.g. hunger) and drives (e.g. food intake). Stimuli (internal or external) adequate to elicit a sensation also elicit activities directed towards reducing the intensity of such sensations, i.e. the stimuli for those sensations induce motivational states that drive the organism, to provide whatever is felt to be lacking. Viewed in this respect, chemosensory signals from food provide the sensory basis of hedonic matrix that controls food acceptance, choice and intake (1). The interfacing of these signals with the changing needs of the organism, include the concept of priorities, competition and compromises in regulation of several factors contributing to homeostasis (2). The fact that an identical stimulus may be handled differently by the nervous system depending upon the variety and complexity of existing variables or the capacity of the nervous system to make continuous appraisals and instant decisions in order that the organism can react in strict accordance with the requirements of internal and external environment, is all well known. Aspects of this inherent plasticity in the nervous system are described below with electro-physiological and behavioural evidence in the domain of feeding behaviour.

Early Studies

The classical paper of Anand and Brobeck (3) showed that tiny discrete lesions of specific, localised zones in hypothalamus bring about aphagia on the one hand, and hyperphagia and obesity

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on the other, depending on the site of the lesion. The main stream of thought during the fifties placed both detection and control of food intake regulation in central nervous structures in which hypothalamus plays a major and decisive role (4). It was gradually realised, however, that though these central nervous structures may play an important part in regulation of feeding behaviour, a number of fundamental questions remain unanswered and point, inter alia, to the existence of peripheral receptor systems involved in food intake and extend well beyond the classic sense of taste and olfaction; and this formed the major thrust of the research activities during the sixties and the seventies.

Alimentary Receptor Systems

Gastric distension, activating distension receptors and simulating a fed state, evoke gastric afferent activity and influence hypothalamic "satiety" and "feeding" centres, the activities bearing an inverse relationship (5). Perfusion of stomach is also shown to activate gastric afferents, and influence selectively localised nervous structures implicated in food intake (6). Probit analysis of response characteristics of the parallel neurons in brain-stem to gastric chemoceptive projections indicates that in addition to 'across-neuron pattern', spatio-temporal cues play an important role in conveying the quality message, while overall height of this pattern seems to indicate the intensity of the test material (7). Further, Sharma and Nasset (8) showed that intestinal perfusion with glucose and aminoacids produced relatively specific features of evoked response in mesenteric nerves, the central projections of which have been localised in hypothalamic regions. Results of this type indicate the existence of peripheral receptor systems in the gut (9), which possibly send information about metabolites in stomach, intestine or portal vein to central nervous structures (10). It is a fast-acting system detecting ingested metabolites and raises serious doubts about detection and control being a central phenomena.

We also know that alimentation requires both instant decisions and continuous appraisal of external elements serving as sensory stimuli for acceptance or rejection of food (e.g. palatability, social context, learned behaviour) and contrasts these factors with internal features such as gastric filling, blood sugar level and the metabolic or "energy pool" of the organism. Once a meal is initiated, its sustenance and termination are linked to the signals that act to monitor subsequent intake, increasing it in the positive feedback loop, or decreasing it in a negative feedback loop (11).

Initially, the oral sensory appraisal of food leads to its acceptance or rejection and, when accepted, is eaten in definite amounts. "This sensory activity to foods is a critical determinant of innate or acquired feeding responses, ensuring an oral selection and a metering of intakes. Through the second step of action of foods in feeding process, these orally determined responses to food are "regulated". At the post absorptive and systemic level, food as a nutrient acts as a metabolic signal on regulatory centres and 'modulates' oral

feeding responses" (12). It could be further suggested that sensory signals not only become important in controlling intake, but feedback into the efferent system controlling the energy pool, producing some of the metabolic changes ordinarily controlled biochemically at cellular level. In common sense terms, it could be hypothesized that the hungry animal eats for taste, and that the taste cues accompanying ingestion directly initiate some of the satiety signals (e.g. hyperglycaemia) which classically follow the normal process of digestion. Thus satiety cues are produced in two phases, first as anticipatory reflex initiated by the taste of food, and secondly by the postabsorptive metabolic events.

The role of gut afferents in ingestion and the possible mechanisms involved have shown a number of features that could be explained on the above basis. We know that administration of endogenous opioids like B-endorphin or encephalin stimulates both feeding and drinking (13) while naloxone, the morphine antagonist, suppresses food and water intake (14, 15), and influences differentially the intake of sweet and sapid substances. The significant reduction in intake of various solutions brought about by naloxone, is observed in animals with intact vagus but not in gastric-vagotomised ones, suggesting the possible involvement of endogenous opioid mechanisms in the gastro-gustatory interactions in taste (16). As peripheral cholinergic blocking does not seem to affect the taste behaviour of the animals, it is quite likely that the changes seen in intakes of sweet and salt solutions in vagotomised animals are predominantly due to the loss of vagal afferents from the stomach (17). The visceral vagal and gustatory afferents, first synapsing in tractus solitarius, project to parabrachial nucleus of pons, and thence to the hypothalamus, amygdala, bed nucleus of striaterminalis and also to the reticular formation. The interactions could be taking place anywhere in these sites. The probability of visceral afferents contributing to the control of ingestive behaviour via the 'solitary-reticular ingestion system' has been suggested, among others, by Norgren (18). The interception of these ingestive signals from the gut could be acting through the gastro-gustatory interaction sites mentioned above and conceivably bring about alteration in the gustatory preferences of the animals.

The flow of information from the alimentary receptors to the brain is not all in one direction but is rather achieved by 'turning' of the receptor systems through use of centrifugal controls. These controls allow sensory pathways to act as variable filters so that stimuli tagged with a particular attribute or feature are alone allowed through for detailed analysis. By such means it is possible to attenuate or amplify afferent signals, or switch on or off the inputs, thereby selecting a particular input at a particular time. These studies have shown that gastric and intestinal sensory mechanisms, operating at the intermediate level between oral and systemic factors, are concerned with the 'sensory' appraisal of food including its texture, viscosity, volume, temperature, and other physicochemical properties of diet. The gastrointestinal mechanism is a fast-acting system and shares in large measure the organisational control characteristics of the oral sensory system (19, 20).

What are the consequences of food ingestion? How does an organism being fed ablib or under conditions of food deprivation, or in varying states of hunger, handle the information from the dietary source? What signals operate before birth when feeding is aquatic and continuous? How are these signals related to the conditions in the adult, where assimilation within the body is also aquatic and continuous? How does the state of 'energy homeokinetics'-surfeit or deficit state, interface with external dietary and environmental cues to guide the feeding behaviour? How indeed feeding fits in the domain described under the rubric of homeostatic motivations? These and allied questions have attracted the attention of several workers during the last few decades. In the following description while global perspective has been kept in mind, work conducted in India has been highlighted and to that extent may show some bias.

Ontogeny of Feeding

Examples of ontogenetic analysis suggest that each stage of development is complete. The common supposition that adult regulations are in some way superior to those of the infant cannot be sustained. Physiological changes do more than keep an animal alive in a constant state, and, when repeated day after day, they alter as time passes and produce the long-term changes of ontogeny. Food and water affects, and is affected by, this adaptability. Observations on ontogeny of saccharine preference in neonate rats clearly suggested that the apparent learning curves for saccharine, were infact maturation curves (11) and were linked to the maturation of gustatory system which is complete by about 14 days of neonatal life of rat (21). It appears that neonate is primarily dependent upon 'taste', rather than 'calories', a feature also seen in adults under certain conditions of nutritional stress, food deprivation, metabolic disorders and psycho-sociocultural overtones.

An alternative possibility has also been proposed. It has been found that the neonate rats ate enough atleast to double the average growth rate if competition for food was eliminated by limiting the litter size. This would indicate that the neonate is primarily dependent on taste cues, and fails to regulate 'calories'. The above results may appear contradictory to the observations in adult animals who are considered to eat for 'calories' (2) and generally regulate body weight over a period of time inspite of the day to day variations in input-output relationship. However, these dissimilarities are, at best, only superficial. Need-related changes in palatability and taste sensitivity are well known. Our approach has been to vary hunger by mealtime restriction, graded food deprivation, insulin or thyroxine injection. We then observed food intake and preference shifts in responses to 'liked' items e.g. fat, glucose or saccharine or 'disliked' items like cellulose, NaCl or quinine which were added to stock diet or put into solution. Normal adult rats and dogs, hypothalamic hyperphagic rats and neonate rats have been used as subjects (1).

Taste Vs. Calories

Studies extended to include other animals than rat and using different methods to vary taste and calories independently have generally confirmed the notion that the importance of taste and calories is related to the state of energy balance: hunger potentiating taste (Figure 1). Physicochemical information from the diet feeds into two detector systems which can respond to signals from taste or calories. It is not a dichotomous system but both sets of cues are acting all the time. Whether the nervous system makes use of either set of signals in monitoring further intake is a function of the state of energy balance. The 'energy pool' acts as a biasing system, assigning priority to taste when the animal is in deficit and to calories when it is in balance or surfeit. The terms used here as 'taste' and 'calories' are infact meant to mean the 'sensory' and the 'metabolic' properties of diet respectively (22). This hypothesis is similar to 'behavioural regulation' hypothesis of Richter, Katz's avidity theory, and Le Magnen's concept of 'primary response' in assuming that organic needs alter perceptual bias on an innate basis so that the animal seeks out and ingests the needed food on the basis of its sensory qualities. The fact that food

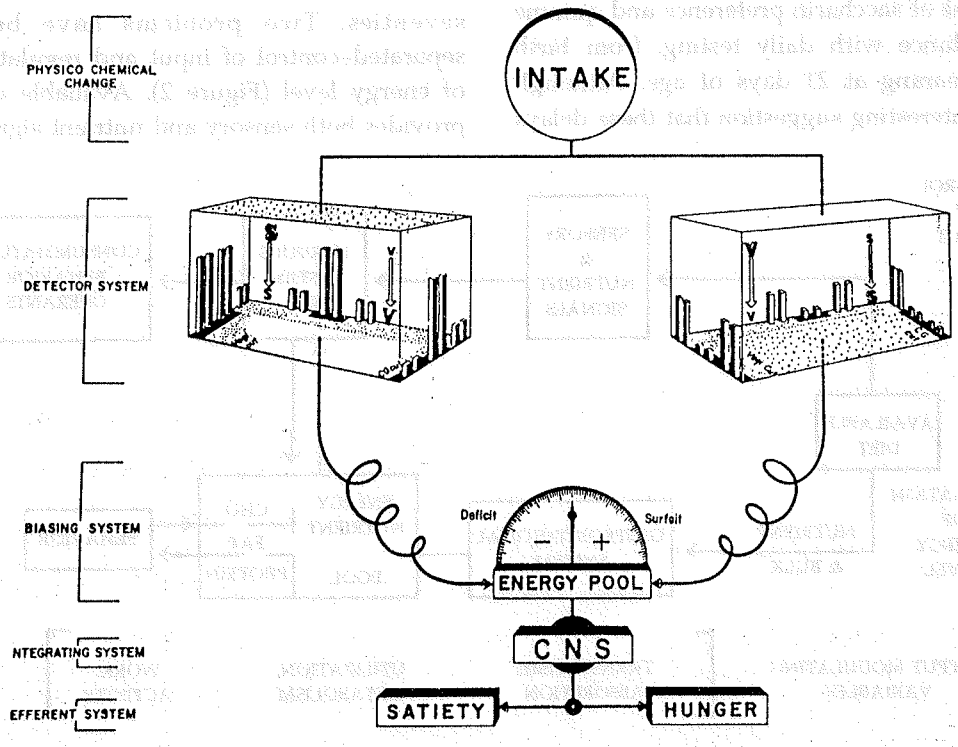

Figure 1. Model showing the dual detector system and the role of the energy pool as a biasing system, in the overall control of food intake (From Sharma et al. J Neural Transmission 33 : 113-154, 1972).

contains nutrients is considered coincidental.

For instance, adapted rats to chronic undernutrition when tested for oral ingestion of various solutions such as glucose, saccharin, sodium chloride, and quinine showed over-reaction of sweeter substances becoming more acceptable, and bitter substances becoming more aversive as a function of increasing degree of chronic food deprivation (23). This has parallels between such effects of food deprivation on gustatory responses and the gustatory responses observed during neonatal stages (11, 20). These results also indicate that there is a gradual development of saccharin preference and quinine avoidance with daily testing, from birth to weaning at 21 days of age. Although the interesting suggestion that these delays may be correlated with differential maturation of taste buds (necessary to discriminate the stimuli) cannot be overlooked, the results also suggest that if such acceptability for sweetness is reinforced, as partially happens with the lactose of mother's milk taken by neonates, this contiguous pairing confers a biological significance in establishing the sweet preference and in regulating intake on the basis of taste.

Control of Input and Regulation of Energy Level

There has been yet another very important dimension added as a result of the studies conducted in sixties and seventies. Two problems have been separated-control of input and regulation of energy level (Figure 2). Available diet provides both sensory and nutrient signals

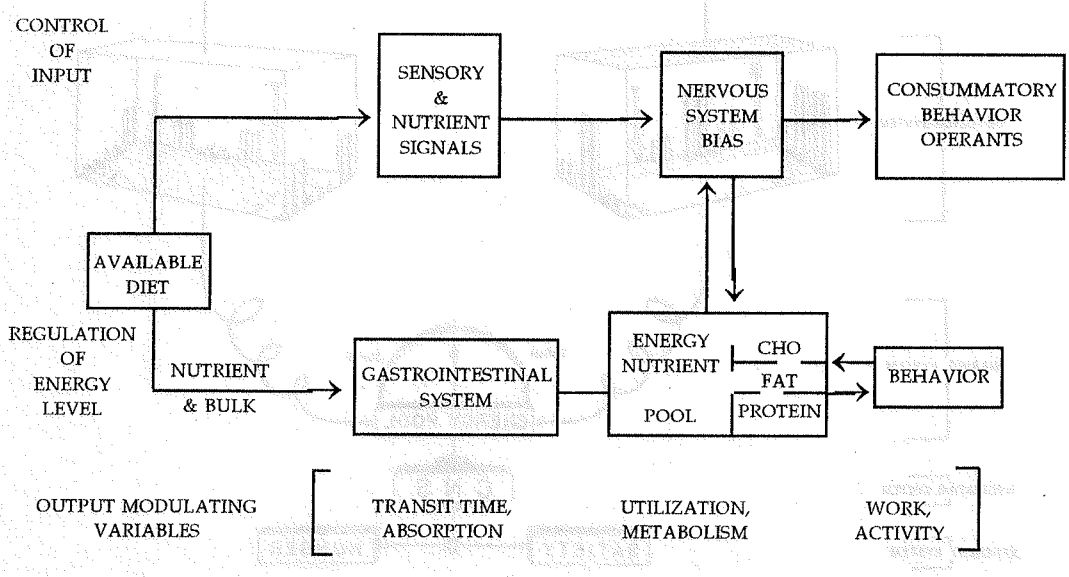

Figure 2. Scheme of input control *(top)* and energy regulation *(bottom)* as interacting systems involved in homeostatic regulation of consummatory behaviour (From : Sharma KN, In : Advances in Physiological Sciences, Macmillan India, 1992, pp 639-647).

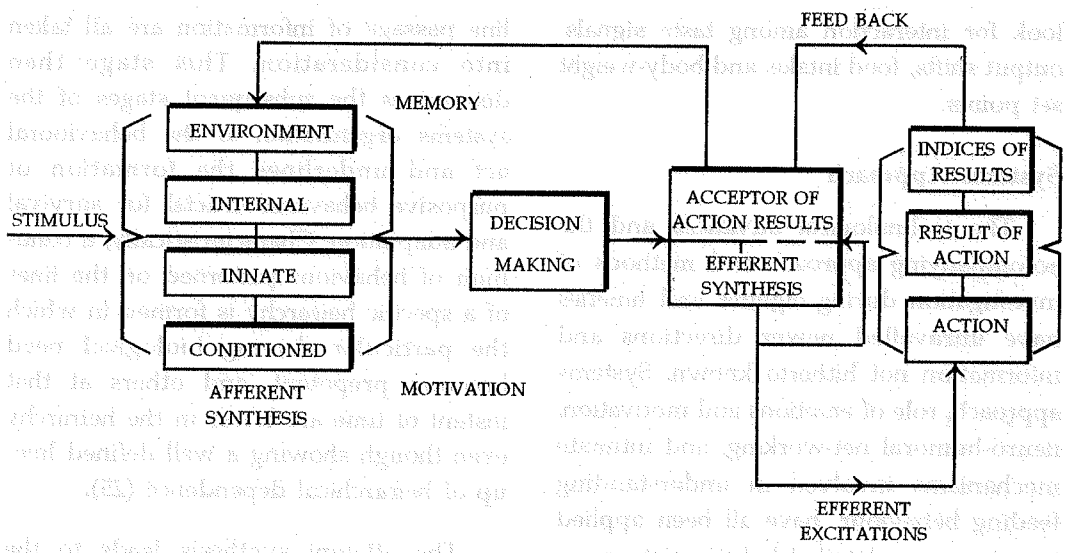

Figure 3. Schematic block diagram showing various interlinked and interacting stages depicting the relationship of stimulus characteristics, afferent synthesis, decision-making, efferent excitations, and the role of feedback control system and memory mechanisms in guiding the motivational behaviour (From : Sharma KN, In : Advances in Physiological Sciences, Macmillan India, 1992, pp 639-647).

that the brain in turn compares to other signals coming from the energy-nutrient pool, which provide information about the sensory and metabolic consequences of these nutrients. The brain then uses this information in modulating food intake (consummatory behaviour) or learned food related behaviour.

One finds that the available diet provides nutrients and bulk going to the body. From this point of view, the regulation of body weight can be effected by a series of output modulating variables, before, during, and after the food enters the energy-nutrient pool. It is easy to see that the combined action of gastric emptying time, intestinal absorption rate, efficiency of food utilisation and metabolic activity, and the behavioural output of muscular work and general activity can be important in regulating the energy-nutrient pool. As the energy pool is modified, it can influence feeding itself by providing appropriate signals as to its condition, which the nervous system uses in the control channel. The sensory signals from available diet and the two-way connecting pathways (vertical arrows) between the control channel and the regulating channel, provide a biological basis for the role of taste in energy exchange, as well as in food intake, by various possibilities of interaction between these channels. Thus in this scheme body weight is not only influenced by food intake and changes in output, but also by taste-induced appetite shifts from energy-nutrient pool (24). The scheme thus biases us to look at the regulation channel more directly than we have in the past and to

look for interaction among taste signals, output shifts, food intake, and body-weight set points.

Systems Approach

The technological advances and the accompanying approach and methods of investigation during eighties and nineties have unravelled newer directions and information not hitherto known. Systems approach, role of emotions and motivation, neuro-humoral net-working, and intimate mechanisms involved in understanding feeding behaviour, have all been applied to get a more detailed holistic picture.

Essentially, homeostatic motivations meet the driving biological needs in the preservation of the species or genus of the individual. The concept of motivation, according to some, is restricted to the analysis of behaviour that is goal directed, or need related, or purposive. Still others define the study of motivation as a search for the determinants of human and animal activity, ranging from systems approach to levels of membrane functioning and molecular and intracellular genetic memory. Each approach has its distinctive value, but is not divorced from the limitations it concurrently poses.

In this complex organisation of systems analysis (Figure 3) afferent synthesis forms the first step in which juxtaposition, selection and synthesizing of functionally diverse inputs linked to the dominant need, past experience or memory, simultaneous presence of other afferent stimuli, and straight through hot-line passage of information are all taken into consideration. This stage then determines the subsequent stages of the systems organisation of the behavioural act and underlines the formation of purposive behaviour crucial for survival and adaptation. Characteristically, a continuum of behaviour patterned on the lines of a specific heirarchy is formed in which the particular driving biological need becomes prepotent, and others at that instant of time are lower in the heirarchy even though showing a well defined line-up of heirarchical dependence (25).

The afferent synthesis leads to the specific state of readiness in which both motivation and environmental stimuli interact as activated by memory mechanisms and bring into focus the preparedness of the organism. This in turn leads to triggering of the behavioural response activation time and determining the whole act to include initial and subsequent stages of decision making, formation of mechanisms of predicting results, and satisfying the specific needs. Dovetailed with this is the next stage of decision-making in a manner that the behavioural act becomes imperative. It is precisely this stage that shapes the significance of resultant activity in need satisfaction, and form the basis of the organism's capability not only to monitor and correct behaviour errors but to bring about behavioural acts to their precise end point. The development of biological motivations appears related to a retrieval of genetic information stored in CNS cells, and can apparently induce such neuronal changes as lead to the activation of DNA and RNA fragments

responsible for synthesing specific polypeptides. This is the process which shapes the pattern of afferent synthesis and decision-making and with which the results of behaviour are constantly compared through feed back influences. Some of the recent findings have laid a fairly good groundwork indicating that the control and regulation of sensory and metabolic events resulting in the particular behavioural act, say, of feeding behaviour, may come from higher levels of the same sensory pathways, from motor pathways, from pathways mediating other modalities and a number of other sources. One of the ways by which this regulation is achieved is by the 'tuning' of receptors through the use of centrifugal controls via short and long feedback loops (22). It may not be difficult to surmise on the basis of such possibilities as to how centrifugal controls, by differently registering and responding to a particular stimulus or set of stimuli, could indeed influence the widely varying spectrum of feeding behaviour.

In a series of recent studies jointly undertaken with the Institute of Normal Physiology, Moscow, the above possibilities have been examined more closely. It has been known that neuronal population in lateral hypothalamus (LH) and the ventromedial hypothalamus (VMH), particularly the units responding to nutrient substance such as glucose, generally behave in a reciprocal manner, and the differential activity levels is linked to the state of hunger or satiety (23). This hypothalamic neuronal activity, influencing motivation of feeding and associated behaviour, can also be differentially influenced by the basal ganglia and frontal cortex supporting the concept of motivational systems guiding behaviour through such modulating influences. The reactivity of sensorimotor cortical (SMC) neurons to micro-iontophoretic application of oligopeptides such as tetragastrin and bradykinin in SMC neurons in hypothalamic-induced food reactions were investigated in unanaesthetised, freely-moving fed rabbits possessing chronically-implanted electrodes. The cortical neuronal activity was recorded in presence or absence of food placed infront of the animal following stimulation of lateral hypothalamus. The results indicate that lateral hypothalamic stimulation induced hunger and the animal would eat vigorously. In such a situation majority of the SMC neurons showed excitatory responses. If, however, LH stimulation was done but food was not placed in front of the animal, the same SMC neurons now predominantly showed an inhibition i.e., non-reinforcement of food, switched the excitatory pattern to inhibitory one. Micro-iontophoretic application of gastrin and bradykinin decreased the percentage of neurons showing activation on LH stimulation in the presence of food, but enhanced the number of positively responding SMC neurons in the absence of food. Thus gastrin and bradykinin produced qualitative changes in SMC neuronal responses to LH stimulation: neurons that initially responsed with activation or inhibition to LH stimulation changed their response in an opposite direction. It would seem that tetragastrin and bradykinin applications lead to specific reorganisation of the neuronal-circuits for

decision-making and theraby differentially influencing the motivational and reinforcing components in the composite feeding behaviour (26, 27).

Appetitive Behaviour in humans

What relevance does this type of behavioural and electrophysiological data in animals have to the observations in humans? The work of Thompson and Campbell (28) on human gustatory responses for both magnitude estimation and hedonic matrix shows a number of features obtainable from animal models. Their studies demonstrated increased hunger ratings as well as enhanced magnitude estimates of pleasantness for sucrose solution following infusion of 2-DG. The results are interpreted to show that 2-DG produces glucoprivation in neuronal units, as shown in experimental animals (29). The change in neuronal activity brings about variation in ingestive behaviour, favouring taste and showing the increased hunger state of the person, analogous to the food-deprived state in animals over-reacting to sensory properties of food (11, 30). The affective behaviour toward a sweet taste in man has been shown to be modified by a variety of changes influencing the internal state of the individual (31). For example, reduction in body weight increased food satisfaction in man and delayed ingestion-induced unpleasantness (30), much in the same manner as chronic food-deprivation in animals potentiated sweet taste. Similarly, insulin-induced hypoglycaemia increases a feeling of hunger in humans (32), which has parallel in insulin-induced gustatory and olfactory potentiation in animals (33). Perceived sensory intensity and hedonic value in neurons has shown important features of gustatory profile linked to internal state of the individual, and has a parallel in animal models (23). These studies thus indicate that nutritional background (internal state), previous dietary history (ontogeny of feeding), and external environmental factors interact in such a way that the prepotent sensory properties of food and experiential factors subserve to bring about relevant metabolic adaptive changes, taste preferences, and food habits.

When these studies were extended to high altitude conditions some interesting aspects have been revealed. Sojourners to high altitude (HA) often complain of anorexia leading to decrease in food intake, and the degree of anorexia seems to be related to the height of ascent. Sensory and metabolic signals from food are known to alter in certain nutritional stresses and one such stress is high altitude exposure, which causes decreases in food intake both in animals and man (1, 34, 35). This decreases in food intake in HA leads to decrease in body weight which is known to influence the food choice and uptake (36, 37). Our recent study (38) was designed to investigate the changes in taste responsiveness in terms of threshold, hedonicity and intensity in Indian soldiers during their stay at an altitude of 3500m. There was a change both in threshold and hedonicity. While threshold was increased, the hedonicity ratings for glucose at HA

were higher than at sea level, indicating increased pleasantness and palatability for glucose. Interviews with the soldiers at HA showed that while they had taken a full plate of food items, they did not feel like eating it after having a few bites. Perhaps it was the altered hedonicity which created this early satiation emanating from a "not-so-palatable" food. Sweet substances and carbohydrate-rich diet improved the appetite. It seems quite certain that once the nutritional stress leads to body weight loss or deficit energy state of the body, hedonics plays a rather prominent role in regulating food intake as observed at high altitude. Quinine sulphate and citric acid thresholds showed a decrease on exposure to HA, and appear to induce aversion at far lower concentrations than could be expected at sea level. This nicely fits with the bimodal model suggested by Jacobs and Sharma (11). The present study further indicates that providing a more palatable carbohydrate-rich diet could to a certain extent, ameliorate anorexia and body weight loss resulting from HA stress.

In conclusion it may be surmised that whether the sensory or the metabolic cues become prepotent to guide the motivated behaviour towards need reduction or homeostatic regulation of feeding, is a dynamic process in which both sets of cues are involved, and it is the interaction of internal milieu with the external environmental factors impinging upon the innate and experiential correlates which appear to determine the degree and the direction of the behavioural act. Thus emotional stress and motivational states can bring about not only a quantitative but a qualitative change in these need related determinants and consequently are expressed in overt forms of behaviour.

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